

# Prednisone plus Methotrexate for Polymyalgia Rheumatica

## A Randomized, Double-Blind, Placebo-Controlled Trial

Roberto Caporali, MD; Marco A. Cimmino, MD; Gianfranco Ferraccioli, MD; Roberto Gerli, MD; Catherine Klersy, MD; Carlo Salvarani, MD; and Carlomaurizio Montecucco, MD, for the Systemic Vasculitis Study Group of the Italian Society for Rheumatology

**Background:** Steroids are the standard treatment for polymyalgia rheumatica. The efficacy of the candidate drug methotrexate has not yet been demonstrated in controlled studies.

**Objective:** To compare the efficacy and safety of prednisone plus methotrexate and prednisone alone in patients with polymyalgia rheumatica.

**Design:** Multicenter randomized, double-blind, placebo-controlled trial.

**Setting:** 5 Italian rheumatology clinics.

**Patients:** 72 patients with newly diagnosed polymyalgia rheumatica.

**Measurements:** The proportion of patients no longer taking prednisone, the number of flare-ups, and the cumulative prednisone dose after 76 weeks.

**Intervention:** Prednisone dosage (25 mg/d) was tapered to 0 mg/d within 24 weeks and was adjusted if flare-ups occurred. Oral methotrexate (10 mg) or placebo, with folic acid supplementation (7.5 mg), was given weekly for 48 weeks.

**Results:** Twenty-eight of 32 patients in the methotrexate group and 16 of 30 patients in the placebo group were no longer taking prednisone at 76 weeks ( $P = 0.003$ ). The risk difference was 34 percentage points (95% CI, 11 to 53 percentage points). Similar results were obtained after adjustment for C-reactive protein level and duration of symptoms in a multivariate model. Fifteen of 32 patients in the methotrexate group and 22 of 30 patients in the placebo group had at least 1 flare-up by the end of follow-up ( $P = 0.04$ ). The median prednisone dose was 2.1 g in the methotrexate group and 2.97 g in the placebo group ( $P = 0.03$ ). The rate and severity of adverse events were similar.

**Limitations:** Follow-up was short, and a high dose of folic acid and a relatively high starting dosage of prednisone were used. Ten of 72 patients (14%) discontinued treatment or were lost to follow-up.

**Conclusions:** Prednisone plus methotrexate is associated with shorter prednisone treatment and steroid sparing. It may be useful in patients at high risk for steroid-related toxicity.

*Ann Intern Med.* 2004;141:493-500.

[www.annals.org](http://www.annals.org)

For author affiliations, see end of text.

See editorial comment on pp 568-569.

Polymyalgia rheumatica is a syndrome that affects older people and is characterized by proximal muscular pain and stiffness. Systemic manifestations and elevated levels of acute-phase reactants are often seen (1, 2). The mainstay of therapy is oral steroids (1-3). Prednisone, 15 to 25 mg, usually suppresses inflammation dramatically (1-9). However, up to 60% of patients experience disease relapse during steroid tapering, and several studies indicate that steroid treatment can only rarely be discontinued before 2 years (2, 3). Higher doses of prednisone are no more effective, but controlled studies have not addressed this issue.

In a large series of patients taking steroids, the median reported starting dosage of prednisone was 20 mg/d (1); Kyle and Hazleman (7) and Ayoub and colleagues (9) reported similar figures. Recent studies indicate that oral steroids should be administered for 18 to 36 months (5-8). The obvious risk for side effects of this long-term treatment, particularly osteoporosis, hypertension, hyperglycemia, and cataracts (4, 5), supports the need for improved therapeutic options, mainly in patients at high risk for steroid-related toxicity (2, 4, 10).

Methotrexate is an effective drug in rheumatoid arthritis, as well as in systemic vasculitis and giant-cell arteritis (11, 12). In addition, several studies have suggested that methotrexate is effective in polymyalgia rheumatica when administered with oral prednisone (13-15). Krall and associates (13) reported the efficacy of methotrexate in 3

cases, and Wagener (14) confirmed this finding in an open-label, nonrandomized trial involving 27 patients. More recently, Ferraccioli and coworkers (15) reported the efficacy of methotrexate as a steroid-sparing agent in an open-label, randomized, controlled study involving 24 Italian patients with classic polymyalgia rheumatica. Only 1 nonrandomized study (16) and 1 randomized, double-blind, placebo-controlled study (17) have failed to find any therapeutic advantage of this drug combination. In Ferraccioli and coworkers' study (15), treatment was discontinued after 12 months in 6 of 12 patients who received methotrexate and steroids but not in any patients treated with steroids alone. Methotrexate was administered with a starting prednisone dosage of 25 mg/d, which was tapered to 0 mg/d within 6 months. These promising results led the Systemic Vasculitis Study Group of the Italian Society for Rheumatology to perform this randomized, double-blind, placebo-controlled, multicenter trial to assess the efficacy and safety of prednisone plus methotrexate in a larger group of patients.

## METHODS

### Patients

Patients with newly diagnosed polymyalgia rheumatica who were consecutively observed from June 1998 to December 1999 were eligible for the study. Five regional

**Context**

Long-term treatment with oral steroids is the mainstay therapy for polymyalgia rheumatica.

**Contribution**

In this double-blind trial, 72 patients with newly diagnosed polymyalgia rheumatica were randomly assigned to receive 48 weekly doses of oral methotrexate (10 mg) or placebo. All received folic acid (7.5 mg/wk) and prednisone (25 mg/d). Prednisone dosages were tapered within 24 weeks or adjusted if disease flared up. At 76 weeks, more patients assigned to methotrexate were steroid-free and fewer had had disease flare-ups compared with those assigned to placebo.

**Implications**

Combining methotrexate with prednisone may decrease the need for long-term steroid therapy in polymyalgia rheumatica.

—The Editors

rheumatology clinics, which receive most of their referrals from general practitioners, participated. The principal investigators responsible for following patients in this study were all rheumatologists.

Polymyalgia rheumatica was diagnosed according to the criteria outlined by Chuang and colleagues (1). Inclusion criteria were age older than 50 years; erythrocyte sedimentation rate greater than 40 mm/h; aching and stiffness at shoulder, hip girdle, or both for more than 1 month; and no signs or symptoms of other musculoskeletal or connective tissue conditions, including elevated levels of serum creatine kinase and polyarthritis (18). Patients with giant-cell arteritis were excluded. Additional exclusion criteria were conditions adversely affected by methotrexate or prednisone treatment, such as chronic hepatitis, liver cirrhosis, or serum aminotransferase levels of more than twice the normal value; chronic lung disease; poorly controlled diabetes mellitus (fasting plasma glucose level  $> 6.66$  mmol/L [ $>120$  mg/dL]); gastric or duodenal ulcer; osteoporotic fractures; peripheral neuropathy; epilepsy; renal failure; poorly controlled hypertension (blood pressure  $> 140/90$  mm Hg); malabsorption; hemolytic or deficiency anemia; platelet count less than  $150 \times 10^9$  cells/L; leukocyte count less than  $3.5 \times 10^9$  cells/L; neutrophil count less than  $1.5 \times 10^9$  cells/L; acute or chronic active infection; history of neoplasia; steroid administration in the previous month; previous therapy with methotrexate or other immunosuppressive agents; or history of long-term alcohol abuse or drug addiction. No concomitant analgesic medications were allowed.

**Study Design**

We conducted an 18-month multicenter, randomized, double-blind, placebo-controlled study comparing the effi-

cacy and tolerability of oral steroids plus methotrexate versus oral steroids alone as first-line treatment in polymyalgia rheumatica. Patients were randomly assigned in a 1:1 ratio to receive prednisone plus methotrexate or prednisone plus placebo. The placebo pills appeared identical to the methotrexate pills.

The ethics committees of the participating centers reviewed and approved the study protocol. Before entering the trial, each patient was informed of the nature, duration, and purpose of the study, as well as of all the potential benefits and drawbacks that could be expected. All participants gave written informed consent.

**Treatment Protocol**

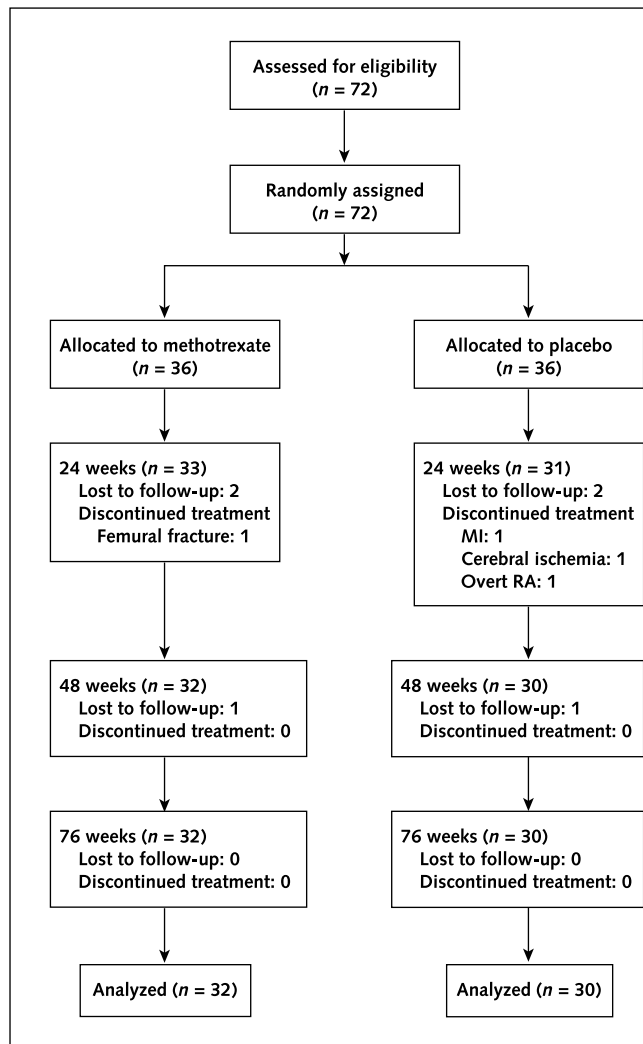
A single weekly dose of oral methotrexate, 10 mg (4 tablets, 2.5 mg each), or placebo was started at diagnosis and maintained for 48 weeks. Adherence to the treatment schedule was assessed by a tablet count of the trial medication during each visit. A single weekly dose of folic acid, 7.5 mg, was administered 24 hours after administration of methotrexate or placebo. All patients received oral prednisone, 25 mg/d, at 8.00 a.m. for the first 4 weeks. Daily doses in the next five 4-week periods were 17.5 mg, 12.5 mg, 7.5 mg, 5 mg, and 2.5 mg. Prednisone treatment was discontinued thereafter. If clinical and laboratory features indicated a relapse, the dose of the previous period was resumed. If polymyalgia rheumatica recurred after steroids were withdrawn, oral prednisone was restarted at the lowest dosage that had previously controlled symptoms. All patients were asked to take oral calcium, 1 g/d, and vitamin D<sub>3</sub>, 800 IU/d.

**Clinical Assessment**

Patients were evaluated before therapy began, every 2 weeks for the first 4 weeks, every 4 weeks from weeks 4 to 24, and every 8 weeks from weeks 24 to 76. Each visit included a complete physical examination and administration of a questionnaire designed to assess symptoms and health status. Adverse events and concomitant therapy were also recorded. To minimize dropouts, we contacted by telephone patients who did not present for follow-up. The principal investigators of each center always assessed clinical evaluations and outcomes, and a co-investigator monitored adverse events and drug delivery.

Blood tests for antinuclear antibody, serum creatine kinase, and hepatitis B and C virus, as well as a latex test for rheumatoid factor, were scheduled at the baseline visit only. Complete blood count, erythrocyte sedimentation rate, C-reactive protein, urinalysis, serum albumin, aminotransferases, alkaline phosphatase, glucose, calcium, urea, and creatinine were tested at the baseline visit and again at each follow-up visit. Trial medication was withdrawn if the leukocyte count dropped below  $3.0 \times 10^9$  cells/L, if the neutrophil count decreased below  $1.3 \times 10^9$  cells/L, if the platelet count decreased below  $100 \times 10^9$  cells/L, if the serum creatinine concentration increased to more than 50% of baseline values or more than 159.12  $\mu$ mol/L

Figure 1. Flow of participants through the study.



MI = myocardial infarction; RA = rheumatoid arthritis.

(>1.8 mg/dL), or if aminotransferase levels exceeded 100% of upper-normal values.

Patients reported adverse events, which were defined as a new diagnosis or incidence of any condition during the treatment protocol, during scheduled visits or at any time throughout the study. Patients were asked which adverse events they experienced at each visit, based on a list of possible adverse events that was read to them. In addition, they were instructed during the first visit to spontaneously report to the investigator any adverse events that occurred during the study.

We defined a flare-up of signs and symptoms of polymyalgia rheumatica (aching and stiffness at shoulder, hip girdle, or both) accompanied by an increased erythrocyte sedimentation rate (>30 mm/h), C-reactive protein level (>5 mg/L), or both as a relapse if it was observed during steroid tapering and as a recurrence if it was observed after steroid withdrawal. The principal investigator assessed re-

lapses and recurrences at every follow-up visit or when an unscheduled visit was requested by patients.

**Outcome Measures**

We planned to attempt to withdraw steroids after 24 weeks of therapy if possible. Efficacy was assessed as the number of patients no longer taking steroids at 76 weeks (primary end point). Secondary outcomes were the number of patients no longer taking steroids at 24 and 48 weeks, the number of patients with disease flare-ups (relapses or recurrences), the total number of flare-ups, the duration of prednisone therapy, the cumulative dose of prednisone, and the number of adverse events.

**Sample Size**

We chose the sample size on the basis of the proportion of patients no longer taking steroids at 76 weeks in recently published series from centers involved in our clinical trial (5, 8, 19). By pooling these data, we expected that approximately 40% of patients in the placebo group would no longer be taking steroids at 76 weeks. Therapy had to perform at least twice as well in the treatment group compared with the placebo group to be considered a clinically important difference. A 2-group chi-square test with a 2-sided significance of 0.05 would have 90% power to detect an assumed difference of 40 percentage points between the placebo and treatment groups when the sample size in each group is 30 or greater. We tentatively increased the sample size to 72 patients, assuming a dropout rate of 20%.

**Randomization and Blinding**

We randomly allocated patients to a treatment group using a 1:1 ratio balanced in blocks. Assignment was not stratified by center. For practical purposes, each center systematically received medication in lots for 10 consecutive patients, and a pharmacist at each center dispensed it. All study personnel and participants were blinded to treatment

Table 1. Demographic Characteristics and Main Baseline Characteristics of the Patients Studied\*

Characteristic	Methotrexate Group (n = 36)	Placebo Group (n = 36)
<b>Demographic</b>		
Age, y	72.5 ± 7.9	72.33 ± 7.28
Women, n (%)	25 (69)	23 (64)
White ethnicity, n	36	36
<b>Clinical features</b>		
Fever, n	12	16
Weight loss, n†	8	7
Peripheral arthritis, n	11	12
Tenosynovitis, n	2	1
Duration of symptoms, mo	3.2 ± 1.4	2.6 ± 1.1
<b>Laboratory features</b>		
Erythrocyte sedimentation rate, mm/h	71.2 ± 24	71.9 ± 19
C-reactive protein level, mg/L	61.4 ± 2.9	78.1 ± 2.6

\* Values presented with a plus/minus sign are means ± SD.

† More than 8% of body weight during the preceding 2 months.

Table 2. Treatment Results throughout the Follow-up Period and at the End of the Study\*

Characteristic	0–24 Weeks			24–48 Weeks		
	Methotrexate Group	Placebo Group	P Value	Methotrexate Group	Placebo Group	P Value
Patients no longer taking prednisone at 24, 48, and 76 wk, n/n	16/32	15/30	0.2	26/32	14/30	0.008
Relapses, n	8	8	–	12	18	–
Recurrences, n	0	0	–	3	11	–
Patients with ≥1 relapse or recurrence, n/n	7/32	8/30	0.2	10/32	19/30	0.02
Duration of prednisone therapy, wk	24†	24†	–	8.5 ± 9.57	13.2 ± 9.97	–
Median duration of prednisone therapy (1st–3rd quartiles), wk	24†	24†	–	4 (0–17)	14 (0–24)	0.09
Total prednisone dose, g	2.10 ± 0.2	2.07 ± 0.2	–	0.32 ± 0.43	0.53 ± 0.54	–
Median prednisone dose (1st–3rd quartiles), g	1.96 (1.96–2.1)	1.96 (1.96–2.1)	0.2	0.07 (0–0.63)	0.367 (0–0.91)	0.11

\* Values presented with a plus/minus sign are means ± SD.

† During the first 24 weeks, all patients received prednisone, as described in the protocol design.

assignment for the duration of the study. Blinding was not formally assessed.

### Statistical Analysis

Continuous variables were reported as the mean ( $\pm$ SD) or as the median and first and third quartiles, if skewed. Frequencies and percentages were calculated for categorical variables. All analyses were based on the intention-to-treat principle. Model assumptions were checked in all cases. A 2-sided *P* value less than 0.05 indicated statistical significance. We used Stata software, version 7 (Stata Corp., College Station, Texas), for all analyses.

### Primary End Point

The proportion of patients no longer taking steroids at 76 weeks was compared according to treatment by using a multivariate, conditional fixed-effects logistic model (with conditioning on study center) while controlling for duration of symptoms and C-reactive protein level. We used the likelihood ratio test to compare the bivariate models containing only the treatment term with the multivariable models. Treatment comparisons were reported as differences in proportions and corresponding 95% CIs, calculated according to Newcombe (20). We excluded treatment-by-center interaction using the likelihood ratio test. All patients who completed follow-up were included (Figure 1).

Because of missing data, 4 of 32 patients in the methotrexate group and 6 of 36 patients in the placebo group were not included in the analysis comparing the percentages of patients no longer taking prednisone (Figure 1). To determine the sensitivity of the results to these missing data, we performed a sensitivity analysis with 3 scenarios: best case (all successes in the methotrexate group and all failures in the placebo group), worst case (the opposite), and intermediate case (50% of successes and failures for each treatment group).

### Secondary End Points

The association between methotrexate treatment and the proportion of patients no longer taking steroids at 24 and 48 weeks, as well as the proportion of patients with relapses or recurrences, was assessed by using the Fisher exact test. The number of flare-ups and adverse events per patient, as well as duration of prednisone therapy and cumulative dose of prednisone, were compared by using the Mann–Whitney U test. The Mann–Whitney U test was also used to compare intermediate assessments (at 24 and 48 weeks) of cumulative doses of prednisone between groups. All patients who completed follow-up were included in the evaluation of secondary end points. For adverse events, all randomly assigned patients were considered.

### Role of the Funding Source

The protocol was funded by a grant from IRCCS Policlinico San Matteo Hospital, after approval of the scientific committee. The funding source had no role in data collection, analysis, or interpretation or in the decision to submit the manuscript for publication.

## RESULTS

### Baseline Characteristics and Follow-up

Thirty-six patients were randomly assigned to receive methotrexate, and 36 were randomly assigned to receive placebo (Figure 1). Main demographic and clinical characteristics of the patients are shown in Table 1. Baseline characteristics were similar between groups, except that patients assigned to placebo had a slightly shorter average duration of symptoms and higher C-reactive protein levels.

In the first 6 months of the study, 2 patients in the methotrexate group and 2 in the placebo group were lost to follow-up. In addition, 1 patient in the placebo group developed overt rheumatoid arthritis and withdrew from the study, and 1 patient in the methotrexate group and 2 patients in the placebo group withdrew before protocol completion because of adverse events. Thus, 33 patients (92%)

Table 2—Continued.

48–76 Weeks			0–76 Weeks		
Methotrexate Group	Placebo Group	P Value	Methotrexate Group	Placebo Group	P Value
28/32	16/30	0.003	28/32	16/30	0.003
0	7	–	20	33	–
4	6	–	7	17	–
4/32	10/30	0.07	15/32	22/30	0.04
5.1 ± 9.43	14.4 ± 12.4		37.75 ± 17.41	51.73 ± 20.12	
0 (0–3)	18 (0–28)	0.004	30 (24–44)	56 (36–72)	0.007
0.19 ± 0.40	0.62 ± 0.72		2.62 ± 0.91	3.22 ± 1.3	
0 (0–0.09)	0.56 (0–0.96)	0.002	2.1 (1.96–2.9)	2.97 (2.17–3.65)	0.03

in the methotrexate group and 31 patients (86%) in the placebo group completed the treatment protocol. Two additional patients (1 taking methotrexate and 1 taking placebo) were lost to follow-up after 48 weeks. At the end of the 76-week follow-up period, 32 patients (89%) in the methotrexate group and 30 (83%) in the placebo group were available for clinical examination. Adherence to treatment, evaluated by tablet count, was optimal in all cases (no tablets were missed during the treatment period).

### Clinical Efficacy

After therapy began, all but 2 patients had complete clinical response with normalization of laboratory features within the first 4 weeks. The 2 remaining patients, both treated with methotrexate, had delayed responses and began prednisone tapering after 8 weeks. The first flare-up was found at week 16 in both groups. Table 2 describes the changes in outcome measures during follow-up and at the end of the study.

### Primary End Point

Sixty-two patients made up the full analysis sample (Figure 1). The proportion of patients who were free of steroids at 76 weeks was higher in the methotrexate group (28 of 32 patients) than in the placebo group (16 of 30 patients) (risk difference, 34 percentage points [95% CI, 11 to 53 percentage points]). After adjustment for duration of symptoms and C-reactive protein levels, similar results were obtained. In a sensitivity analysis, the risk difference was 44.4 percentage points (CI, 23.1 to 60.8 percentage points) in the best-case scenario, 30.6 percentage points (CI, 9 to 48.6 percentage points) in the intermediate-case scenario, and 16.7 percentage points (CI, 4.5 to 36 percentage points) in the worst-case scenario.

### Secondary End Points

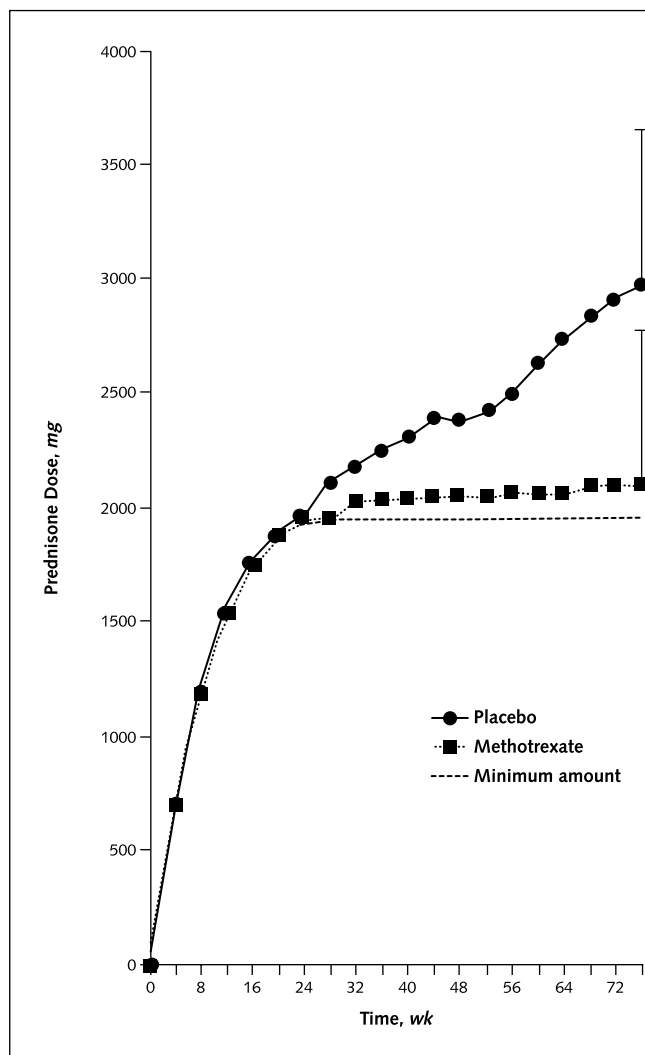
All 62 patients in the full analysis sample were considered. The proportion of patients no longer taking steroids at 24 weeks was 50% in both groups, while the efficacy of therapy was higher in the methotrexate group at 48 weeks (81% vs. 47%). The proportion of patients who experi-

enced 1 or more flare-ups (relapse or recurrence) was lower in the methotrexate group (47% vs. 73%). The number of flare-ups per patient was lower in the methotrexate group than in the placebo group (27 episodes vs. 50 episodes;  $P = 0.009$ ). Four patients (2 in the methotrexate group and 2 in the placebo group) showed relapse of mild symptoms without laboratory evidence of relapse; these events were not considered flare-ups. Both duration of prednisone therapy and total dose of prednisone were also significantly lower in the methotrexate group at week 76. Figure 2 shows the median cumulative prednisone dose throughout follow-up.

### Adverse Events

All 72 randomly assigned patients were included in the analysis of adverse events. Forty-two adverse events were recorded in patients treated with methotrexate, and 34 adverse events were recorded in patients taking placebo (Table 3) ( $P > 0.2$ ). However, the same proportion of patients experienced adverse events in both groups (26 of 36 patients;  $P > 0.2$ ). When gastrointestinal symptoms were grouped, the proportion of affected patients was higher in the methotrexate group than in the placebo group, although not significantly so (8 patients with 12 events and 3 patients with 4 events, respectively;  $P = 0.19$ ). The severity of gastrointestinal adverse events was reported as mild in all but 1 patient, who was receiving methotrexate and developed a moderately severe episode of melena. Methotrexate was withdrawn because of adverse events in 1 patient who had a femur fracture after major trauma. Two patients in the placebo group withdrew from the treatment protocol because of myocardial infarction and cerebrovascular ischemic disease, respectively. No patient developed cytopenia or reduction in hemoglobin levels, and no elevated levels of liver enzymes required withdrawal from the study. Transient, slight elevation of serum aminotransferase levels was found in 1 patient treated with methotrexate and in 2 patients treated with placebo. Two patients in the placebo group had increased blood fasting

**Figure 2.** Median cumulative dose of prednisone in the methotrexate group and the placebo group compared with the lowest amount scheduled by treatment protocol.



Vertical bars represent 75th percentiles.

glucose levels, which were treated by diet alone in 1 and by diet plus oral glibenclamide in the other.

## DISCUSSION

This randomized, double-blind, placebo-controlled trial shows that the proportion of patients with polymyalgia rheumatica who were free of steroids at 76 weeks was higher in the methotrexate plus prednisone group (28 of 32 patients) than in the placebo plus prednisone group (16 of 30 patients). Results from the sensitivity analysis supported the main analysis, although in the worst-case scenario statistical significance was not reached. The proportion of patients who experienced 1 or more flare-ups was lower in the methotrexate group than in the placebo group (47% vs. 73%), as was the total number of flare-ups (27 episodes vs. 50 episodes).

The only previous randomized, double-blind, placebo-controlled study on the efficacy of methotrexate in polymyalgia rheumatica yielded disappointing results. This probably resulted from the short duration of methotrexate treatment, the high number of dropouts (19 of 40 patients), and the low dosage of methotrexate used (17). By contrast, the open-label study of Ferraccioli and coworkers (15), which represented the basis for our present trial, showed that methotrexate had good efficacy. A new feature of our study was the addition of folic acid to the treatment protocol to avoid unnecessary side effects in an elderly patient sample. This approach was recently supported by the results of a large controlled trial in patients with rheumatoid arthritis (21), which showed that folate supplementation decreased the incidence of elevated aminotransferase levels and made interruption of methotrexate therapy less likely. In that study, patients received 2.5 to 5 mg of folic acid per week; we chose to administer 7.5 mg/wk because only 7.5-mg tablets are available in Italy.

Our positive results are in keeping with those of a similar study by Jover and colleagues (12) in patients with giant-cell arteritis. In that study, methotrexate therapy was started at a weekly dose of 10 mg and was continued for 24 months. A remarkable similarity between our study and that of Jover and colleagues is that the steroid-sparing effect of methotrexate was seen only at long-term follow-up. In contrast, 2 other studies of patients with giant-cell arteritis showed no advantage of adding methotrexate to standard steroid therapy (22, 23). The first examined a small series of patients treated late in the course of their disease with 7.5 mg of methotrexate per week (22). In the second study (23), steroid dosages were rapidly tapered to an alternate-day schedule, which is less effective than the daily regimen (24). More important, follow-up lasted only 12 months, whereas the adjunctive effect of methotrexate observed by us and by Jover and colleagues (12) was seen

**Table 3.** Adverse Events Observed during the Study

Adverse Event	Methotrexate Group (n = 36), n	Placebo Group (n = 36), n
Weight gain*	4	2
Urinary tract infection	7	6
Hypertension	5	3
Tachycardia	0	2
Other cardiovascular disorders	3	5
Fracture	2	1
Other musculoskeletal symptoms	2	1
Neuropsychiatric disorders	3	5
Dyspepsia	6	2
Nausea or vomiting	1	1
Diarrhea	2	0
Stomatitis	1	0
Other gastrointestinal symptoms	2	1
Alopecia	1	0
Diabetes mellitus	0	2
Exacerbation of cataract†	0	2
Other	3	1

\* More than 5% of body weight at the screening visit.

† Evidenced by blurring of vision. Confirmed by an ophthalmologist in all cases.

only after the first year. Furthermore, despite the comparable incidence of treatment failures between groups, fewer relapses in the form of isolated polymyalgia rheumatica occurred in the methotrexate group (12). This finding, although in a different setting, is in keeping with our results.

In our study, mild gastrointestinal symptoms were more common in methotrexate-treated patients and the overall incidence of adverse events was similar between groups. We did not find any substantial reduction in steroid-related toxicity in the methotrexate group despite the lower cumulative dose of prednisone used. This probably reflects the low incidence of steroid-related side effects in our study. In fact, our selection criteria excluded most of the patients at high risk for steroid toxicity. Also, 18 months of follow-up may be insufficient to detect many steroid-related side effects; the average time from therapy initiation to appearance of a first side effect has been reported as 1.6 years (4). Although no patients withdrew from our study because of methotrexate-related laboratory abnormalities, patients treated with methotrexate should be monitored according to the usual guidelines for rheumatoid arthritis.

Our study was not specifically designed to quantify the steroid-sparing effect of methotrexate. However, in patients treated with this drug, the cumulative prednisone dose decreased by more than 25% over an 18-month period. Such reduction should be especially advantageous in patients with diabetes mellitus, hypertension, glaucoma, osteoporotic fractures, and other disorders negatively affected by higher steroid doses.

Our study has several limitations. First, we followed patients for only 18 months. Second, we used a relatively high starting dosage of prednisone and tapered it rapidly over 24 weeks, which may have contributed to the high incidence of flare-ups in the first 12 months of follow-up. Third, 10 of 72 patients (14%) discontinued treatment or were lost to follow-up. Finally, we used a high dose of folic acid, which may have reduced both the efficacy of methotrexate and the incidence of methotrexate-related adverse events.

In conclusion, our data suggest that combination therapy with prednisone and methotrexate can be effective in polymyalgia rheumatica when methotrexate is administered for at least 1 year from disease onset at a dosage of at least 10 mg/wk. This schedule can reduce the incidence of flare-ups and the amount of prednisone required to maintain remission. Our findings could be of practical importance in the clinical setting, particularly in patients who cannot tolerate high doses of prednisone. Further studies should address the efficacy of methotrexate as induction therapy and examine whether methotrexate supplementation may allow lower initial doses of prednisone.

From the University of Pavia, Pavia, University of Genoa, Genoa, University of Udine, Udine, University of Perugia, Perugia, and Arcispedale Santa Maria Nuova, Reggio Emilia, Italy.

**Note:** Drs. Caporali and Cimmino contributed equally to the manuscript.

**Acknowledgments:** The authors thank Franco Barattini, Opera Contract Research Organization, for supporting the trial; Vanni Bascapè, Pharmacology Department at Policlinico San Matteo, for manufacturing the placebos; and Carlo Pesce, MD, PhD, for reviewing the manuscript.

**Grant Support:** By Società Italiana di Reumatologia and IRCCS Policlinico San Matteo.

**Potential Financial Conflicts of Interest:** None disclosed.

**Requests for Single Reprints:** Roberto Caporali, MD, Divisione di Reumatologia, Policlinico San Matteo, Piazzale Golgi 2, 27100 Pavia, Italy; e-mail, caporali@smatteo.pv.it.

Current author addresses and author contributions are available at [www.annals.org](http://www.annals.org).

## References

1. Chuang TY, Hunder GG, Ilstrup DM, Kurland LT. Polymyalgia rheumatica: a 10-year epidemiologic and clinical study. *Ann Intern Med.* 1982;97:672-80. [PMID: 6982645]
2. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med.* 2002;347:261-71. [PMID: 12140303]
3. Kyle V, Hazleman BL. Treatment of polymyalgia rheumatica and giant cell arteritis. I. Steroid regimens in the first two months. *Ann Rheum Dis.* 1989;48:658-61. [PMID: 2782975]
4. Gabriel SE, Sunku J, Salvarani C, O'Fallon WM, Hunder GG. Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica. *Arthritis Rheum.* 1997;40:1873-8. [PMID: 9336424]
5. Cimmino MA, Moggiana G, Montecucco C, Caporali R, Accardo S. Long term treatment of polymyalgia rheumatica with deflazacort. *Ann Rheum Dis.* 1994;53:331-3. [PMID: 8017988]
6. Gran JT. Current therapy of polymyalgia rheumatica [Editorial]. *Scand J Rheumatol.* 1999;28:269-72. [PMID: 10568422]
7. Kyle V, Hazleman BL. The clinical and laboratory course of polymyalgia rheumatica/giant cell arteritis after the first two months of treatment. *Ann Rheum Dis.* 1993;52:847-50. [PMID: 8311533]
8. Salvarani C, Boiardi L, Mantovani V, Ranzi A, Cantini F, Olivieri I, et al. HLA-DRB1 alleles associated with polymyalgia rheumatica in northern Italy: correlation with disease severity. *Ann Rheum Dis.* 1999;58:303-8. [PMID: 10225816]
9. Ayoub WT, Franklin CM, Torretti D. Polymyalgia rheumatica. Duration of therapy and long-term outcome. *Am J Med.* 1985;79:309-15. [PMID: 4036982]
10. Ferraccioli GF, Di Poi E, Damato R. Steroid sparing therapeutic approaches to polymyalgia rheumatica-giant cell arteritis. State of the art and perspectives. *Clin Exp Rheumatol.* 2000;18:S58-60. [PMID: 10948766]
11. Langford CA, Sneller MC, Hoffman GS. Methotrexate use in systemic vasculitis. *Rheum Dis Clin North Am.* 1997;23:841-53. [PMID: 9361158]
12. Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2001;134:106-14. [PMID: 11177313]
13. Krall PL, Mazanec DJ, Wilke WS. Methotrexate for corticosteroid-resistant polymyalgia rheumatica and giant cell arteritis. *Cleve Clin J Med.* 1989;56:253-7. [PMID: 2743546]
14. Wagener P. [Methotrexate therapy of polymyalgia rheumatica]. *Z Rheumatol.* 1995;54:413-6. [PMID: 8578892]
15. Ferraccioli G, Salaffi F, De Vita S, Casatta L, Bartoli E. Methotrexate in polymyalgia rheumatica: preliminary results of an open, randomized study. *J Rheumatol.* 1996;23:624-8. [PMID: 8730115]
16. Feinberg HL, Sherman JD, Schrepferman CG, Dietzen CJ, Feinberg GD.

The use of methotrexate in polymyalgia rheumatica. *J Rheumatol*. 1996;23:1550-2. [PMID: 8877923]

17. van der Veen MJ, Dinant HJ, van Booma-Frankfort C, van Albada-Kuipers GA, Bijlsma JW. Can methotrexate be used as a steroid sparing agent in the treatment of polymyalgia rheumatica and giant cell arteritis? *Ann Rheum Dis*. 1996;55:218-23. [PMID: 8733437]

18. Caporali R, Montecucco C, Epis O, Bobbio-Pallavicini F, Maio T, Cimmino MA. Presenting features of polymyalgia rheumatica (PMR) and rheumatoid arthritis with PMR-like onset: a prospective study. *Ann Rheum Dis*. 2001;60:1021-4. [PMID: 11602472]

19. Salvarani C, Cantini F, Macchioni P, Olivieri I, Niccoli L, Padula A, et al. Distal musculoskeletal manifestations in polymyalgia rheumatica: a prospective followup study. *Arthritis Rheum*. 1998;41:1221-6. [PMID: 9663479]

20. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med*. 1998;17:873-90. [PMID: 9595617]

21. van Ede AE, Laan RF, Rood MJ, Huizinga TW, van de Laar MA, van Denderen CJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multi-center, randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 2001;44:1515-24. [PMID: 11465701]

22. Spiera RF, Mitnick HJ, Kupersmith M, Richmond M, Spiera H, Peterson MG, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin Exp Rheumatol*. 2001;19:495-501. [PMID: 11579707]

23. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum*. 2002;46:1309-18. [PMID: 12115238]

24. Hunder GG, Sheps SG, Allen GL, Joyce JW. Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. *Ann Intern Med*. 1975;82:613-8. [PMID: 1137255]

---

**Current Author Addresses:** Drs. Caporali and Montecucco: IRCCS Policlinico San Matteo, Piazzale Golgi 2, 27100 Pavia, Italy.

Dr. Cimmino: Department of Internal Medicine, Viale Benedetto XV, 16100 Genova, Italy.

Dr. Ferraccioli: Division of Rheumatology, School of Medicine, Catholic University of the Sacred Heart—CIC, Via Moscatti 31, 00168 Rome, Italy.

Dr. Gerli: 1st Medicina Interna e Scienze Oncologiche, Policlinico Monteluce, 06122 Perugia, Italy.

Dr. Klersy: Direzione Scientifica, IRCCS Policlinico San Matteo, Piazzale Golgi 2, 27100 Pavia, Italy.

Dr. Salvarani: Azienda Ospedaliera, Via Umberto I 50, 42100 Reggio Emilia, Italy.

**Author Contributions:** Conception and design: R. Caporali, M.A. Cimmino, G. Ferraccioli, R. Gerli, C. Salvarani, C. Montecucco.

Analysis and interpretation of the data: R. Caporali, M.A. Cimmino, G. Ferraccioli, R. Gerli, C. Klersy, C. Salvarani, C. Montecucco.

Drafting of the article: R. Caporali, M.A. Cimmino, C. Montecucco.

Critical revision of the article for important intellectual content: R. Caporali, M.A. Cimmino, G. Ferraccioli, R. Gerli, C. Salvarani, C. Montecucco.

Final approval of the article: R. Caporali, M.A. Cimmino, G. Ferraccioli, R. Gerli, C. Klersy, C. Salvarani, C. Montecucco.

Provision of study materials or patients: R. Caporali, M.A. Cimmino, G. Ferraccioli, R. Gerli, C. Salvarani, C. Montecucco.

Statistical expertise: C. Klersy.

Obtaining of funding: R. Caporali, C. Montecucco.

Collection and assembly of data: R. Caporali, C. Klersy, C. Montecucco.